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Proposed Registration Decision PRD2017-01

Nicarbazin

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Overview

Proposed Registration Decision for Nicarbazin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Nicarbazin (technical product), 30% Granulated Nicarbazin Premix (manufacturing concentrate), and OvoControl P (commercial class end-use product), containing the technical grade active ingredient nicarbazin, to reduce feral pigeon populations.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Nicarbazin, 30% Granulated Nicarbazin Premix, and OvoControl P.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on nicarbazin, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on nicarbazin, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Nicarbazin?

Nicarbazin is the active ingredient found in OvoControl P bait which is used to decrease pigeon populations by reducing egg hatch. Nicarbazin is made up of two chemical components: DNC (4,4' -dinitrocarbanilide) and HDP (2-hydroxy-4,6 dimethylpyrimidine). DNC is the active component while HDP increases absorption of the complex by the pigeons. Nicarbazin is also registered as a veterinary drug for use against a disease in chickens called coccidiosis, which is cause by the parasite *Eimeria*.

Health Considerations

Can Approved Uses of Nicarbazin Affect Human Health?

Nicarbazin is unlikely to affect human health when used according to label directions.

Potential exposure to nicarbazin may occur when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human populations (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100 times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

Registrant-supplied acute, short, and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature and regulatory reviews from other countries were assessed for the potential of nicarbazin to cause acute, chronic, reproductive and developmental toxicity, and various other effects. The available toxicology studies indicate

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

nicarbazin is of low acute toxicity via the oral route, is mildly irritating to the eyes,is non-irritating to the skin and is not a dermal sensitizer. It is not genotoxic.

While OvoControl P works by reducing the number of eggs that hatch, the reproductive effect is limited to pigeons that directly consume the bait. The effect is not permanent and normal egg hatch resumes in pigeons once feeding on the bait is discontinued. Long-term studies in laboratory animals show that nicarbazin is not developmentally toxic. The reproductive effect occurs at levels that will not be encountered by animals other than pigeons. Therefore, when the product is used according to the proposed label directions, reproductive effects on animals other than pigeons are not expected.

The risk assessment protects against the potential hazards by ensuring that the level of exposure to humans is well below the lowest dose at which such effects occurred in tests conducted on laboratory animals.

Residues in Water and Food

Dietary risks from food and water are not of concern.

As there are no food uses for OvoControl P, dietary exposure will be low. Exposure to residues of nicarbazin in drinking water through run-off and secondary exposure to bird droppings and eggs is also expected to be low. Consequently, no risk due to exposure from food or drinking water is expected.

Risks in Residential and Other Non-Occupational Environments

Estimated risk for non-occupational exposure is not of concern.

Nicarbazin is proposed for use as a reproductive inhibitor by reducing egg hatch in feral pigeon populations. The product will be used outdoors in areas with limited public access. The application directions on the product label will ensure that the bait is distributed in such a way that left-over bait is not anticipated. Consequently, while risk to the general population is not a concern due to the low toxicity of nicarbazin, it is not expected that adult, youth and children will be exposed to nicarbazin.

Occupational Risks from Handling OvoControl P

Occupational risks are not of concern when OvoControl P is used according to label directions, which include protective measures.

To protect workers from exposure to the end-use product, the precautionary label statements indicate that contact with skin, eyes, and clothing must be avoided as well as breathing of dusts (i.e., fines from the pellet). The label also states that applicators must wear a long-sleeved shirt, long pants, shoes plus socks, gloves, and protective eyewear. Precautionary and hygiene statements on the label are considered adequate to protect individuals from occupational exposure.

Environmental Considerations

What happens when Nicarbazin is introduced into the environment?

Nicarbazin and its two components, DNC and HDP, are not expected to pose risks of concern to the environment when OvoControl P is used according to the label directions.

Nicarbazin can enter the environment when used as a bait to control local populations of feral pigeons by reducing the number of eggs that hatch. OvoControl P pellets are consumed by feral pigeons that have learned to feed at the location where bait is to be used (on roof tops or paved areas) at a specific time each day. OvoControl P is dosed based on the number of pigeons being targeted so that all the bait pellets are consumed within one hour of application. Environmental exposure to soil and water from uneaten pellets is expected to be limited. If nicarbazin does reach soil it is expected to be broken down slowly by microbes. It is expected to bind to soil particles and have a low potential to move deeper through soil.

When OvoControl P is eaten by pigeons, its components (DNC and HDP) are released in feces and urine, respectively, and are expected to be deposited in localized areas (for example, on buildings and sidewalks where pigeons roost). DNC and HDP can reach the aquatic environment through droppings sporadically getting into water. The fate of nicarbazin, DNC and HDP in water is unknown; however, the overall exposure to the aquatic environment is expected to be limited.

Nicarbazin is not acutely toxic to birds or other terrestrial and aquatic organisms. Effects on birds are limited to the reduction of egg hatch caused by DNC and the effects are reversible. Daily exposure to non-target birds from bait pellets is not expected, because the bait is consumed quickly by the target pigeons. Exposure to birds of prey or scavengers is also expected to be minimal since the DNC found in pigeon tissue is not easily absorbed and no effects are expected from HDP.

To protect non-target bird populations, label statements requiring users to monitor pigeon baiting locations for the presence of non-target birds will be required. As a precaution, label statements to prevent direct exposure to waterbodies adjacent to baiting locations are required.

Considering the use pattern of OvoControl P, it is expected that all the bait pellets will be eaten by the target pigeons within an hour of feeding. Nicarbazin will not be available to be eaten by non-target organisms and will not enter adjacent water bodies or soil. Secondary exposure to the nicarbazin components, DNC and HDP, from consumption of treated pigeons is also not a concern. The environmental risk resulting from the use of nicarbazin as a pigeon bait is expected to be negligible.

Value Considerations

What is the Value of OvoControl P?

OvoControl P is bait that is eaten by adult pigeons to prevent their eggs from hatching. It is used with other control methods to reduce feral pigeon populations.

Pigeons cause a wide range of problems which may impact the health and well-being of people (for example, by acting as disease carriers). OvoControl P represents an alternative method of reducing pigeon populations.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of OvoControl P to address the potential risks identified in this assessment are as follows:

Key Risk-Reduction Measures

Human Health

To prevent irritation to skin, and eyes, anyone distributing OvoControl P must wear a long-sleeved shirt, long pants, shoes plus socks, gloves, and protective eyewear.

Environment

Label statements will be required to prevent exposure to adjacent water bodies and to prevent consumption by non-target organisms.

Next Steps

Before making a final registration decision on nicarbazin, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

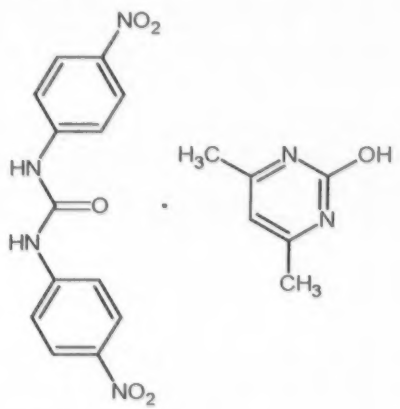
When the PMRA makes its registration decision, it will publish a Registration Decision on nicarbazin (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Nicarbazin

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Nicarbazin
Function	Bird contraceptive
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	1,3-bis(4-nitrophenyl)urea-4,6-dimethylpyrimidin-2-ol (1:1)
2. Chemical Abstracts Service (CAS)	urea, *N*,*N*'-bis(4-nitrophenyl)-, compd. with 4,6-dimethyl-2-pyrimidinol (1:1)
CAS number	330-95-0
Molecular formula	$C_{19}H_{18}N_6O_6$
Molecular weight	426.38
Structural formula	
Purity of the active ingredient	98.0%

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product - Nicarbazin Technical

Property	Result
Colour and physical state	Light yellow solid
Odour	Characteristic odour
Melting range	270°C
Boiling point or range	Not applicable
Density	0.5 g/mL (packing density)
Vapour pressure	Expected to be negligible at ambient temperature.
Ultraviolet (UV)-visible spectrum	No absorbance at $\lambda > 450$ nm
Solubility in water	Insoluble in water
Solubility in organic solvents	Slightly soluble in dimethylsuphoxide and dimethylformamide, insoluble in methanol and water but decomposes slowly when mixed with them.
n-Octanol-water partition coefficient (K_{ow})	Not required
Dissociation constant (pK_a)	No dissociable moiety
Stability (temperature, metal)	Stable when exposed to heat and light. Acidic and basic conditions caused some decomposition. Some splitting of the nicarbazin complex into separate moieties was apparent but further decomposition of these moieties was not observed.

End-Use Products

Property	30% Granulated Nicarbazin Premix	OvoControl P
Colour	Yellow to brown	Yellow to yellowish-tan
Odour	Not required	Non to slight grain odour
Physical state	Solid	Solid
Formulation type	Granular	Pellet
Guarantee	Nicarbazin 30%	Nicarbazin 0.5%
Container material and description	Multi-wall paper bags with an inner aluminum foil liner; approx. 90 × 45 × 15 cm.	Multi-walled lined paper bags, 13.61 kg
Bulk density	0.529 – 0.705 g/mL	0.512 – 0.576 g/mL
pH of 1% dispersion in water	5 - 7	Not applicable
Oxidizing or reducing action	Not applicable	Not applicable
Storage stability	Stable when stored for 5 years in its packaging material at 25°C and 60% humidity.	Stable when stored for 5 years in its packaging material at 25°C and 60% humidity.
Corrosion characteristics	Not corrosive to the packaging material.	Not corrosive to the packaging material.
Explodability	Not explosive	Not explosive

1.3 Directions for Use

OvoControl P bait is applied as a broadcast treatment either by hand or by mechanical feeders at an application rate of 5 grams bait/pigeon. It is applied to flat roof tops or other flat surfaces of structures in areas with limited public access where pigeons are found. To determine the required amount to apply in an area, flock counts must be performed prior to application. OvoControl P bait is to be used with other methods of pigeon control in an Integrated Pest Management (IPM) program.

1.4 Mode of Action

Nicarbazin prevents egg hatch by interfering with the formation of the vitelline membrane that separates the egg yolk and egg white. It is also registered as a veterinary drug for use in chickens to control a disease called coccidiosis.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulations has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

No methods are required to quantify residues of nicarbazin since there are no food uses.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

The PMRA conducted a detailed review of the toxicological database for nicarbazin. The database consists of an array of laboratory animal (in vivo) and cell culture (in vitro) toxicity studies currently required for hazard assessment purposes. As nicarbazin is used as a veterinary drug in the broiler chicken industry, the foreign reviews of nicarbazin as a feed-additive for veterinary use were provided and were also utilized in the risk assessment. Although several of the submitted studies were old and conducted prior to the implementation of modern Good Laboratory Practices (GLP) and testing guidelines, none of the deficiencies are considered sufficient to exclude their use in this assessment. The scientific quality of the data is acceptable, and the database is considered adequate to characterize the toxicity of nicarbazin.

The toxicological database for nicarbazin included studies with the Koffogran, a poultry feed additive containing nicarbazin, which is similar to the manufacturing concentrate that is used for

formulating the end-use product. In other studies, the test substance was the individual components of nicarbazin, 4,4'-dinitrocarbanilide (DNC) and 2-hydroxy-4,6-dimethylpyrimidine (HDP), rather than the complex nicarbazin. Since absorption of DNC is greatly improved when it is complexed with HDP as nicarbazin, chronic toxicity may have underestimated the potential due to insufficient absorption.

Metabolism and toxicokinetics of nicarbazin was addressed in older studies (dated 1977–1986) conducted in chickens (four studies) and in the rat (one study). None of the studies fully addressed the current test guidelines for absorption, tissue distribution, metabolism and excretion and the level of data reporting was lacking compared to current standards. Therefore, while the individual studies were classified supplemental, when the studies were taken together, the totality of all the information was deemed to meet the data requirements.

Metabolism of nicarbazin is similar in the chicken and the rat. Upon ingestion, nicarbazin dissociates into its individual components, DNC and HDP. The components are metabolised separately and behave differently. DNC is mainly excreted in the feces, while HDP is absorbed and eliminated in the urine. Both components of nicarbazin are absorbed at low levels into the tissues, with residue concentrations of DNC being higher than those of HDP. Metabolism of the HDP component is limited and it is the major compound in urine and tissues. Following withdrawal of the test substance from the diet, HDP is rapidly eliminated from tissues.

The metabolic pathway of DNC involves the reduction and acetylation of one or both nitro groups yielding M3, N-[4-[[[(4-nitrophenyl)amino]carbonyl] amino]phenyl]acetamide and M1, N,N'-[(carbonyl-diimino)di-4,1-phenylene]bis[acetamide], respectively. A minor metabolite, M2, recovered from excreta, resulted from the cleavage of the BNPU molecule and was identified as N, N'-1,4-phenylenebis(acetamide).

Nicarbazin is of low acute oral toxicity in mice and rats. Based on the Material Safety Data Sheet (MSDS) for Nicarbazin Technical the oral LD_{50} (rat) is >5000 mg/kg bw. Nicarbazin was mildly irritating to the eyes, non-irritating to skin and is not a dermal sensitizer.

A request to waive the requirement for an acute dermal toxicity study was accepted based on the available toxicological database for nicarbazin, including no signs of toxicity in a dermal irritation study and an overall low acute toxicity profile, as well as the long documented history of commercial use of nicarbazin as an anticoccidial feed additive for broiler chickens without reports of adverse effects in workers. Exposure to the product by applicators, which is bait in the form of a pellet, can also be limited with the wearing of appropriate personal protective equipment, such as gloves.

The submitted acute inhalation toxicity study was insufficient because the particle size of the test substance was considered to have been too large to have reached all regions of the respiratory tract. A replacement study was, however, not required because of the low toxicity profile of nicarbazin, the long history of commercial use of nicarbazin without reports of adverse health effects, and the limited potential for inhalation exposure as the end-use product is formulated as a pellet and is for outdoor use only.

In a two-year dietary toxicity study in the rat, HDP and DNC showed low chronic toxicity. There were no treatment-related effects with respect to mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, or gross and histologic pathology (including tumours).

In a chronic toxicity study, groups of pure bred beagles were fed a diet containing the HDP and DNC, components of nicarbazin, for one hour a day, for six days a week, for 24 months. Bile duct proliferation and elevated serum glutamic pyruvic transaminase (SGPT) levels were reported in the high dose group but further investigations revealed no hepatic abnormalities. There were no compound related effects with respect to mortality, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, or gross and histologic pathology (including tumours).

In a prenatal developmental toxicity study in the rabbit, there were no effects on mortality, clinical signs, body weight, food consumption or caesarean parameters. Based on prominent lobulation of the liver, the maternal NOAEL was 60 mg/kg bw/d. None of the observed fetal abnormalities (i.e., visceral or skeletal minor alterations/variants or major fetal malformations) were considered to be directly related to treatment. The offspring developmental toxicity NOAEL was 120 mg/kg bw/d (the highest dose tested).

Two reproductive toxicity studies in the rat were submitted. Both studies were considered supplementary due to the general lack of reporting details (for example, dose selection criteria, male reproductive performance parameters) and the low number of animals per test group. However, in both studies nicarbazin did not adversely affect growth or reproduction performance of males or females through three generations.

Although nicarbazin was weakly mutagenic in bacterial mutagenicity tests without metabolic activation, it was not genotoxic in mammalian systems including an in vivo micronucleus test, a mouse lymphoma assay, nor in an unscheduled DNA synthesis assay in hepatocytes. Consequently, nicarbazin is considered to not be genotoxic.

The results of the toxicology studies conducted in vitro and on laboratory animals with nicarbazin are summarized in Appendix I Table 1.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. In addition, the general public, medical community, government and non-governmental organizations are able to report pesticide incidents directly to the PMRA. Specific information regarding the mandatory reporting system regulations under the *Pest Control Products Act* can be found at http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/incident/index-eng.php.

Since nicarbazin is a new active ingredient pending registration for use in Canada, no incident reports have been submitted to the PMRA as of 20 April 2016. Once products containing - nicarbazin are registered, the PMRA will monitor for incident reports.

Nicarbazin is registered in the United States and three human incidents involving nicarbazin were reported to the United States Environmental Protection Agency (USEPA) between 1 January 2010 to 4 February 2015. The incidents were classified as minor severity (USEPA Memorandum: Nicarbazin: Tier I Review of Human Incidents, 26 May 2015), and, thus, do not have an impact on this assessment.

3.2 Determination of Acute Reference Dose

3.2.1 Dermal Absorption

No information was provided on the dermal absorption of nicarbazin. The dermal absorption of nicarbazin is expected to be low since the product is a solid pellet.

3.2.2 Use Description

OvoControl P is a commercial product that will be used to reduce egg hatch in feral pigeon populations in urban outdoor spaces. The use is limited to feral pigeons and the product will be distributed only in areas that have limited public access, such as rooftops of malls, hospitals, rail yards, schools and commercial buildings, as well as manufacturing facilities and industrial parks. This product is not to be used in agricultural settings.

It is formulated as a ready-to-use pellet containing 0.5% w/w nicarbazin as the active ingredient. Based on the risk assessment and conditions of use, a restricted-entry interval is not proposed, nor required, for this product.

The pellets will be scattered on flat, paved surfaces by manual broadcast applications or, for larger pigeon flocks (that is, , > 50 birds), using a mechanical feeder. OvoControl P must be supplied to pigeons throughout the nesting period, which can be seasonal or year-round depending on the climate.

The application rate is 5 g/bird. In order to deliver the correct amount to the flock, a flock count is performed prior to the intended time of application. The label use directions specify not to apply more OvoControl P than the pigeons will eat in a single feeding. An OvoControl program begins with a pre-baiting period with cracked corn. Also a conditioning process (lasting 5–30 days) is carried out, whereby, OvoControl P is applied by the intended method of application, each day at approximately the same time, to train the pigeons to consume the bait. The product will not be applied if non-target feeding persists and/or cannot be prevented. Based on these use directions, the bait will be readily consumed by birds at each feeding and direct environmental exposure from left-over bait is expected to be low.

3.2.3 Mixer, Loader, and Applicator Exposure and Risk

Occupational exposure to OvoControl P is expected to be short term and predominantly by the dermal routes, and to a lesser extent by the inhalation and ocular routes, when the product is being distributed in outdoor spaces. The product is a ready-to-use bait that is applied directly to the areas where pigeons flock/feed. For mechanical feeders, the bait will be loaded to the machine before application but there is no mixing involved.

The toxicity of the active ingredient is low and it is mildly irritating to eyes. However, the end-use product contains an impurity from carry-over during manufacturing that poses a health concern for dermal, inhalation and ocular exposure. To provide additional protection to workers, precautionary statements will be included on the labels to warn users that the product may cause skin and eye irritation and that it is harmful if inhaled. The labels will also warn users to avoid contact with skin and eyes, and to avoid breathing dust. Standard personal protective equipment for commercial applicators (including a long-sleeved shirt, long pants, shoes plus socks, and gloves), as well as the requirement for eye protection (based on the results from testing), will also protect workers from exposure to the impurity.

Exposure for workers to nicarbazin, and to any impurities in theend-use product, is not anticipated to present a health risk of concern due to the low toxicity of the active ingredient and the reduced occupational exposure when label directions are followed.

3.2.4 Post-application Exposure and Risk

Post-application exposure is low since the product is distributed in such a way that left-over bait is not anticipated. The physical form of the bait (a pellet) also minimizes exposure for workers (compared to dusts or liquids, for example) in the event that some left-over bait remains in the treated areas. A restricted re-entry interval is not required.

3.2.5 Residential and Bystander Exposure and Risk

Residential and bystander exposure is not expected when the end-use product is used according to the label directions. The product is to be applied by authorized personnel in secured areas with limited public access (for example, rooftops or other flat paved surfaces).

The label directions require that a conditioning period be carried out whereby a small quantity of bait (1 g/bird) is initially applied each day, at approximately the same time, to train the pigeons to consume the bait upon distribution. This amount is gradually increased over several days to achieve the target dosage of 5 g/pigeon (bird). In this manner, left-over bait is not expected after a feeding.

3.3 Determination of Acceptable Daily Intake

3.3.1 Food

As there are no food uses for OvoControl P, dietary risk to humans from the use of OvoControl P is not of concern.

3.3.2 Drinking Water

Although the end-use product will not be applied near or directly to water, some drinking water exposure may be possible through run-off from treated areas since the bait will be applied outdoors onto impervious surfaces such as rooftops, and pavement in manufacturing facilities and industrial parks.

Secondary exposure to the environment may also arise from pigeon droppings (containing nicarbazin) and eggs of birds consuming the bait. Upon ingestion in birds, nicarbazin dissociates into the individual components DNC and HDP, and the components follow separate metabolic routes. Neither DNC nor HDP undergo significant metabolism and both are excreted predominantly unchanged in the feces and urine, respectively.

HDP is water-soluble and absorbs visible light and will degrade rapidly in the environment by photolysis, while DNC is non-mobile in soil, binding tightly to soil and feces. In either case, exposure to residues of complexed and uncomplexed nicarbazin in drinking water from the application of the OvoControl P is expected to be low and will not pose a health risk of concern.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Calculations of acute reference doses (ARfDs) and acceptable daily intakes (ADIs) are not required for nicarbazin. Based on all the available information and hazard data, nicarbazin is considered to be of low toxicity. Thus, there are no threshold effects of concern. As a result, there is no need to apply uncertainty factors to account for intra- and interspecies variability, or have a margin of exposure required. Further factoring of consumption patterns among infants and children, special susceptibility in these subpopulations to the effects of nicarbazin, including developmental effects from pre- or post-natal exposures, and cumulative effects on infants and children of nicarbazin and other registered products containing nicarbazin, does not apply to this active ingredient. As a result, the PMRA has not used a margin of exposure approach to assess the risks of nicarbazin to human health.

3.3.4 Aggregate Exposure and Risk

The use pattern of OvoControl P is limited to use as bait for feral pigeons. Based on all the relevant information in the PMRA files, there is reasonable certainty that no harm will result from aggregate exposure of residues of nicarbazin to the general Canadian population, including infants and children, when the end-use product is used as labelled. This includes all anticipated dietary (food and drinking water) exposures and all other non-occupational exposures (dermal and inhalation) for which there is reliable information.

3.3.5 Maximum Residue Limits (MRLs)

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine that the consumption of the maximum amount of residues that are expected to remain on food products when a pesticide is used according to label directions will not be a concern to human health. This maximum amount of residues expected is then legally specified as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of adulteration provision of the *Food and Drugs Act*. Health Canada specifies science-based MRLs to ensure the food Canadians eat is safe.

As there are no food uses proposed for OvoControl P, specification of a MRL will not be required for nicarbazin.

3.4 Antimicrobial Resistance Assessment

No health risk of concern is expected due to the development of antimicrobial resistance from the use of nicarbazin as a reproductive inhibitor for feral pigeons.

Nicarbazin is not registered in Canada or in the United States as a human drug. The activity of nicarbazin is specific to protozoa and the veterinary drug shows no antimicrobial activity against bacteria.

The potential for nicarbazin resistance to develop in protozoa from the use of OvoControl P is limited by the low level of exposure to the external environment. While OvoControl P will be distributed outdoors as a bait, it is limited to use in outdoor settings on paved areas with limited public access and all the bait will be consumed at each feeding. This product is not to be used in agricultural settings.

In humans, protozoan infections are most often related to imported fresh produce or untreated drinking water. The prevalence of protozoan species in an urban setting is expected to be much lower than that in an agricultural setting which could harbour a number of protozoan species. Since many protozoan species are obligate intracellular parasites, the external environment is mainly exposed to non-infective oocysts (excreted in the host feces) which will not select for resistance. Furthermore, the level of environmental exposure from the use of OvoControl P is much lower than that arising from poultry manure management practices. Nicarbazin is used in the poultry industry on a regular basis and despite decades of extensive use, the prevalence of nicarbazin resistance is relatively low.

While humans can be infected with protozoan parasites, the prevalence of clinical cases is low. Most protozoan species are host-specific. Infections in humans are mostly self-limiting and treatment is often not required. When treatment is required, antibiotics such as metronidazole, tinidazole, sulphamethoxazole and trimethoprim, and nitazoxanide are effective. The use pattern for OvoControl P is limited to feral pigeons and there are no uses that directly target humans. Since the label requires personal protective equipment (PPE) for workers, the overall exposure of workers to nicarbazin will be low. Consequently, the likelihood that the use of OvoControl P would promote nicarbazin resistance in human protozoan species is low, and not of concern.

Since species of *Eimeria* are common parasites of feral pigeons there is the potential for nicarbazin-resistant *Eimeria* species to arise in pigeons that ingest OvoControl P. Nicarbazin resistance in feral pigeons does not pose a health concern because clinical infections in pigeons are rare and treatment is uncommon. Also, since *Eimeria* species are host-specific, species that infect pigeons will not infect poultry. *Eimeria* species do not infect humans. Even if nicarbazin resistance were to develop, it would not be of concern since there are many other classes of anti-coccidial drugs available to the poultry industry (for example, ionophores, quinolones, guanidine derivatives, etc.) that would still be effective. Consequently, the likelihood that the use of OvoControl P would promote the development of nicarbazin resistance in the poultry industry is low and not of concern.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Nicarbazin is insoluble in water and volatility is expected to be very low. Nicarbazin, DNC and HDP are stable to hydrolysis at a range of pH (pH 5 to 9). When exposed to light for 24 hours, nicarbazin did not break down in aqueous solution. Furthermore, DNC adsorbs to soil and was observed to adsorb to surfaces of test vessels demonstrating its affinity to partition to solids. Based on available information, nicarbazin, DNC and HDP are not expected to transform due to abiotic processes particularly when used as pellets.

In soil, biotransformation of nicarbazin proceeded with DT_{50} values of approximately 28–119 days. A DT_{90} was not observed, as 28-30% of the initial concentration of nicarbazin was still present after a year in laboratory studies. A terrestrial field dissipation study also indicated nicarbazin is persistent in soil (DT_{50} of 301 days). A lack of detection below 15 cm depth in soil in a field dissipation study indicates nicarbazin is expected to remain in the top layers of soil. No transformation products other than DCN and HDP were identified in the studies. Studies on biotransformation in water were not available; however, based on the results in soil, stability of nicarbazin to hydrolysis and DNC's affinity to adsorb to surfaces, biotransformation in aqueous solutions is also not expected to be significant, and is unlikely to be a major route of transformation in the aquatic environment.

When consumed by birds, nicarbazin disassociates into DNC and HDP. Both DNC and HDP are excreted within days and are not significantly metabolised. HDP is excreted in the urine while DNC is insoluble in water and excreted in feces. DNC adsorbs readily to surfaces and is expected to bind to fecal matter.

For a summary of the fate and behaviour of nicarbazin in the environment see Appendix I, Table 3.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (such as, protection at the community, population, or individual level).

Pellets containing nicarbazin (DNC and HDP) are broadcast over small areas on roof tops or flat, paved/concrete surfaces in urban areas. Pigeons will be pre-conditioned to the feeding stations and bait is deployed such that all bait will be consumed in a short period of time immediately after dispersal. Based on this use pattern, environmental exposure resulting from the use of OvoControl P is expected to be limited. EECs in soil and water were not calculated and the risk assessment was based on a qualitative estimate of exposure.

When nicarbazin is ingested by birds, DNC and HDP dissociate. Both DNC and HDP are eliminated from the bird within days when nicarbazin is withdrawn from the diet. DNC and HDP are excreted separately in feces and urine, respectively. Exposure to non-target organisms could occur through consumption of pellets not eaten by the targeted birds and through consumption of treated pigeons. DNC and HDP could enter water or soil through pigeon droppings (feces and urine); however, this is not expected to be significant.

4.2.1 Risks to Terrestrial Organisms

Available studies regarding toxicity to terrestrial species are summarized in Appendix I, Table 4. Nicarbazin is not acutely toxic to the organisms tested. Terrestrial plants, populations of beneficial arthropods and populations of invertebrates, such as earthworms and bees, are not expected to be significantly exposed to residues of nicarbazin and risk to these organisms is considered negligible.

Nicarbazin is practically nontoxic to birds and mammals on an acute basis (oral and dietary). There is a long history of nicarbazin use as a veterinary drug in the production of broiler chickens to treat coccidiosis, a common parasitic infection of the intestinal tract caused by coccidian protozoa. Inhibition of egg hatchability in birds is reversible once nicarbazin is removed from the diet and returns to normal within 7 to 14 days. Targeted pigeons must consume the nicarbazin-treated pellets on a daily basis for the effects of nicarbazin to be realized and pigeon populations to be controlled. Although it is expected that nicarbazin would prevent egg hatch in all avian species if exposed on a continual basis, incidental or occasional consumption would not pose a reproductive risk. Habitual feeding and long-term exposure of wild mammals is also not expected.

OvoControl P bait is limited for use on roof tops or on flat paved or concrete surfaces, away from water, and is broadcast within a small radius once per day at each station. Each targeted pigeon flock is preconditioned to feed at a baiting location/station at a specific time each day prior to use of OvoControl P. Dosing rates are established during the conditioning stage such that all the OvoControl P bait is entirely consumed by the target flock within one hour of feeding, and dosing rates are adjusted based on monitored pigeon flock size to ensure that all bait is consumed. Therefore, no significant amount of bait is left unconsumed, after the feeding period, for consumption by non-target species (birds or mammals). To further mitigate exposure to non-target birds, periodic monitoring during feeding/deployment of bait is required to ensure non-target species are not being exposed (i.e., consuming bait), and use must be discontinued if non-target species cannot be prevented from feeding. In addition, label instructions indicate OvoControl P must be protected from excessive rain and standing water. This will prevent entry of residues into water adjacent to baiting locations.

Terrestrial organisms can be exposed to nicarbazin residues through pigeon droppings containing DNC and HDP. The majority of droppings is expected to be limited to localized areas where pigeons roost (for example, on buildings and sidewalks); however, pigeons are expected to visit other sites as well, which can result in environmental exposure to treated pigeon droppings containing DNC and HDP. This exposure is expected to be sporadic, of limited magnitude and should pose negligible risk to non-target terrestrial organisms.

Secondary exposure of predators or scavengers to nicarbazin through consumption of treated pigeons, or their eggs, is not expected to be significant. Effects through this route are not expected as birds and mammals eating treated pigeons are unlikely to be exposed on a daily basis and DNC and HDP will dissociate once in the gut of the pigeon. The long history of use of nicarbazin in broiler chickens for human consumption and the well-documented metabolic fate of nicarbazin and its components (HDP and DNC) have demonstrated that nicarbazin is no longer biologically available once consumed by the birds. Available data indicates that the bioavailability of DCN is at least 33 times lower when dissociated from HDP. The lack of DNC bioavailability makes it extremely unlikely that avian predators/scavengers could consume sufficient amounts of treated pigeon on a daily basis for reproductive effects to be observed.

Based on this environmental risk assessment, the risk to non-target terrestrial organisms when OvoControl P is used as per label instructions is expected to be negligible.

4.2.2 Risks to Aquatic Organisms

Available studies regarding aquatic toxicity testing with HDP and DNC are summarized in Appendix I, Table 5. No study was provided to assess the toxicity of the complex nicarbazin (DNC:HDP in equimolar proportion) to non-target aquatic organisms. The reported water solubility for DNC is between 51.70 and 75.95 µg/L, and was observed to be even lower in aquatic toxicity studies (maximum achievable test concentration, 20 µg/L). Thus, for all tests conducted with DNC, the highest test concentration was at the observed limit of solubility. Studies with *Daphnia*, freshwater fish (rainbow trout, bluegill sunfish, and guppy), and fresh water algae (*Chlorella)* indicated that HDP was practically nontoxic to aquatic organisms on an acute basis. No acute toxicity effects were observed for DNC up to the observed limit of solubility, indicating that acute toxicity is not a concern for aquatic organisms.

Although nicarbazin itself was not tested, exposure to aquatic habitats is expected to be minimal based on the use pattern. As a precaution, however, label statements will be required to direct users to prevent exposure to aquatic environments by deploying bait on roof tops or flat paved or concrete surfaces, keeping feeding stations at least six metres away from any body of water, and by not applying the product directly to water. Furthermore, it is expected that all of the bait will be consumed by the target pigeon flock in less than one hour after dispersal.

Exposure to DNC and HDP from treated pigeon droppings falling into water is expected to be incidental and limited. Furthermore, when in water, HDP is highly soluble and will disperse quickly in aquatic environments. DNC would be expected to partition to surfaces, for example, to sediments and plants, making it less available to be taken up by aquatic organisms.

In summary, exposure to non-target aquatic organisms from the proposed use of OvoControl P will be minimal and risks of concern to the aquatic environment are negligible when used as per label instructions.

4.2.3 Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. In addition, the general public, medical community, government and non-governmental organizations are able to report pesticide incidents directly to the PMRA. Specific information regarding the mandatory reporting system regulations under the *Pest Control Products Act* can be found at http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/incident/index-eng.php.

Environmental incident reports are obtained from two main sources, the Canadian pesticide incident reporting system (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the USEPA Ecological Incident Information System (EIIS).

There have been no environmental incidents involving nicarbazin in the USEPA EIIS database, as of October 6, 2016. When products containing nicarbazin are registered in Canada, the PMRA will continue to monitor for incident reports

5.0 Value

Pigeons cause problems such as damaging structures and aircrafts, contaminating food and feed, and providing a source of disease (for example, histoplasmosis) and allergens.

Several methods are often needed to manage pigeon populations. Most control methods target adult pigeons rather than egg hatch, including the use of 4-aminopyridine which is registered as bait. Non-chemical methods of controlling adult pigeons include trapping, repellents (for example, polymerized butenes, scare devices), exclusion and removal of food sources. An alternative to reduce hatch is physical destruction of eggs. OvoControl P is to be used with other control strategies to decrease pigeon populations. It is an alternative method of decreasing pigeon populations because it targets egg hatch rather than adult birds.

Value information consisted of efficacy data from four studies and use history. Small cage trials demonstrated OvoControl P bait reduced the total number of pigeon eggs that hatched by 59%. Normal egg hatch resumed once feeding on OvoControl P bait was discontinued. Operational trials demonstrated that the use of OvoControl P decreased pigeon populations by 53% starting within the first year. Further population declines were observed in each subsequent year of OvoControl P baiting with an 81 to 88% reduction in two to four years. The use of nicarbazin bait is compatible with other control strategies (for example, exclusion). Published information from the United States provided further evidence to support the value of OvoControl P in decreasing pigeon populations by reducing egg hatch when used with other pigeon control methods.

The value information supports the claim that OvoControl P reduces egg hatch in pigeons and subsequently decreases the pigeon population when applied according to the directions for use. It is to be used as part of an Integrated Pest Management Program because multiple techniques are needed for pigeon control.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, nicarbazin and its components, DNC and HDP, were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Nicarbazin does not meet all Track 1 criteria, and is not considered a Track 1 substance.

No transformation products were reported.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

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5 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 -Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

8 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

- Nicarbazin and the end-use product, OvoControl P, do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The end-use product does contain wheat, soy and fish which are identified in *Canada Gazette*-Part 2 as allergens known to cause anaphylactic reactions. The product label will be amended to include the standard allergen statements.

An impurity, which is not on one of the above noted lists, is present in OvoControl P and poses a health concern for dermal, inhalation and ocular exposure. Mitigative measures (including standard personal protective equipment and precautionary statements) specified on the label adequately address this health concern.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for nicarbazin is adequate to define the toxic effects that may result from exposure. Metabolism of nicarbazin involves dissociation into its individual components, DNC and HDP. DNC is mainly excreted in the feces, while HDP is eliminated in the urine. Both components of nicarbazin are absorbed in the tissues in low levels, with residues of DNC being higher than those of HDP. The metabolic pathway of DNC has been established.

Nicarbazin was of low acute toxicity in laboratory animals via the oral route, mildly irritating to the eyes, non-irritating to skin and it is not a dermal sensitizer. Based on the long history of commercial use of nicarbazin and formulation of the product is in a pellet form which will be distributed outdoors by workers wearing personal protective equipment, health effects from dermal and inhalation exposure are not expected. Nicarbazin is also not a developmental toxicant, nor a genotoxicant.

Loaders, applicators, and workers are not expected to be exposed to levels of nicarbazin that will result in an unacceptable risk due to exposure when OvoControl P is used according to label directions. Bystander and post-application exposure is also low since the product will only be used on pigeons and the bait will be quickly consumed by the pigeons. Consequently, bystander and post-application exposure is not of concern.

An impurity is present in OvoControl P which poses a health concern. Mitigative measures (including standard personal protective equipment and precautionary statements) specified on the label adequately address this health concern.

There are no food uses for OvoControl P and exposure to residues of nicarbazin in drinking water through run-off and secondary exposure to bird droppings and eggs is expected to be low. Consequently, dietary risk to humans will be low and not of concern when the product is used according to label instructions.

Nicarbazin is used as a veterinary drug in the poultry industry against coccidiosis caused by *Eimeria* species. The level of exposure from the use for feral pigeons will be much lower than that resulting from the manure management practices in the poultry industry. As *Eimeria* species are obligate intracellular parasites, it is non-infective oocysts that are excreted in the host feces. Exposure to nicarbazin at this stage of the life cycle does not select for resistance in *Eimeria* species. Consequently, the development of resistance in *Eimeria* species from exposure to nicarbazin in the environment is not of concern. If resistance were to develop, it would not be of concern since there are many other anti-coccidial veterinary drugs available that would still be effective against *Eimeria* species.

As the end-use product contains wheat, soy and fish, which are identified as allergens, the product label will be amended to include the standard allergen statements.

7.2 Environmental Risk

Nicarbazin (in the form of OvoControl P bait) is expected to be used on rooftops or other paved areas and will be entirely consumed by the target pigeon flock during daily preconditioned feeding periods (less than one hour), thus minimizing the potential for the exposure of nicarbazin to soil, water and non-target organisms. There are no risks expected from pigeon feces or from consumption of treated pigeons by predators or scavengers. Precautionary label statements will be required to prevent exposure of non-target organisms and their habitats. When used according to label statements for OvoControl P, nicarbazin and its components (HDP and DNC) are not expected to pose risks of concern to the environment.

7.3 Value

Pigeons cause a wide range of problems which may impact the health and well-being of people (for example, by acting as disease carriers). OvoControl P is an alternative method of decreasing pigeon populations by reducing egg hatch. It is used with other methods to manage pigeon populations.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Nicarbazin (technical product), 30% Granulated Nicarbazin Premix (manufacturing concentrate), and OvoControl P (commercial class end-use product), containing the technical grade active ingredient nicarbazin, to reduce pigeon populations.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

♀	female
♂	male
>	greater than
≥	greater than or equal to
λ	wavelength
%	percent
℃	degrees Celsius
µg	microgram(s)
a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
BAF	bioaccumulation factor
BCF	bioconcentration factor
BNPU	N, N'-bis-(4-nitrophenyl)urea
bw	body weight
CAS	Chemical Abstracts Service
CD/CRJ	Cohen diabetic/ Charles River (Japan)
CEPA	*Canadian Environmental Protection Act*
cm	centimetre(s)
d	day(s)
DIR	Regulatory Directive
DMSO	dimethylsulfoxide
DNC	4,4'-dinitrocarbanilide
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
EC_{50}	effective concentration on 50% of the population
EEC	estimated environmental concentration
EIIS	USEPA Ecological Incident Information System
FDRL	Food and Drug Research Laboratories
g	gram(s)
GLP	Good Laboratory Practices
HDP	2-hydroxy-4,6-dimethylpyrimidine
IPM	Integrated Pest Management
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
M1	N,N'-[(carbonyl-diimino)di-4,1-phenylene]bis[acetamide]
M2	N, N'-1,4-phenylenebis(acetamide)
M3	N-[4-[[[(4-nitrophenyl)amino]carbonyl] amino]phenyl]acetamide

mg	milligram(s)
mL	millilitre(s)
MAS	maximum average score
MIS	maximum irritation score
MRL	maximum residue limit
MSDS	Material Safety Data Sheet
NA	not applicable
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOI	Notice of Intent
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
rec+	recombinant positive
rec-	recombinant negative
SFO/2	single-first order, two parameter exponential decay
SGPT	serum glutamic pyruvic transaminase
TSMP	Toxic Substances Management Policy
US	United States
USD	unscheduled DNA synthesis
USEPA	United States Environmental Protection Agency
UV	ultraviolet
w/w	weight per weight dilution

Appendix I Tables and Figures

Table 1 Acute Toxicity of Nicarbazin Technical

Study Type/Animal/PMRA #	Study Results
Acute toxicity	
Acute Oral Toxicity Rat PMRA# 2502340	LD_{50} (♂ & ♀) = 5000 mg/kg bw Low acute oral toxicity
Acute Dermal Toxicity Data-waiver request PMRA# 2502359	1) the lack of toxicity in a dermal irritation study 2) an overall low acute toxicity profile 3) the long history of commercial use of nicarbazin Waiver request granted
Toxicokinetic Study	
Metabolism Rat, Fisher [^{14}C]-BNPU-nicarbazin[1] PMRA# 2502370	Metabolism in the rat is the same as in the chicken. No sex dependent differences in the metabolism.
Metabolism Chicken, Hubbard cross broiler [^{14}C]-BNPU-nicarbazin[1] in a gelatin capsule PMRA# 2502370	> 95% of the radioactive dose was excreted within 72-hours. Nicarbazin (BNPU) is readily excreted into feces. No sex-dependent differences.
Metabolism Chicken [^{14}C]-BNPU-nicarbazin[1] PMRA# 2502370	In the excreta, the majority of the radioactivity in the excreta was the parent compound BNPU, with small quantities of M1, M2 and M3 (qualitative analysis). BNPU-nicarbazin is metabolised and absorbed in the tissues, and the main metabolites have been identified.
Metabolism Chicken [^{14}C]-nicarbazin, labelled in the DNC or HDP moiety PMRA# 2502370	Metabolism of the DNC and HDP components of nicarbazin behave independently. The DNC moiety is mainly excreted unchanged in the feces, while the HDP moiety is eliminated unchanged in the urine. In tissues, residues of DNC are higher than residues of HDP.
Metabolism Chicken, Hubbard broiler	HDP accounted for a large majority of the radioactivity in the excreta (> 85.0%), kidney (84.0%) and liver (89.0%). The relative distribution (as % of the total radioactive dose) of radioactivity in the excreta and tissues was not determined.

Study Type/Animal/PMRA #	Study Results
[^{14}C]-HDP-nicarbazin[2]	HDP metabolised to a limited extent in chickens. It is absorbed in tissues, and excreted in the urine primarily as unchanged HDP.
Chronic Toxicity	
24-month chronic toxicity (dietary) Rat, FDRL PMRA# 2502364	NOEL > 400 mg/kg bw/d No evidence of chronic toxicity Non-GLP study
24-month chronic toxicity (dietary) Dog, Beagle PMRA# 2502365	NOEL = 240 mg/kg bw/d (6 d/week) based on bile duct proliferation and elevated SGPT levels. No evidence of chronic toxicity Non-GLP study
Reproductive and developmental toxicity	
Developmental toxicity (oral) Rabbit, New Zealand White PMRA# 2648954	Maternal Toxicity: NOEAL= 60 mg/kg bw/d based on prominent lobulation of all liver lobes which were also seen at 200 mg/kg bw/d and 400 mg/kg bw/d in the range-finding study. Offspring Toxicity: NOAEL =120 mg/kg bw/d, the highest dose tested.
Developmental toxicity (oral) Rat, CD/CRJ PMRA# 2502366	A NOEL cannot be determined The study was partially translated and non-GLP.
Multigeneration reproductive toxicity (dietary) Rat, Merck colony PMRA# 2502367	Parental, Reproductive, and Offspring NOAEL 0.04% in the diet (not presented in terms of mg/kg bw/d) No adverse effects on growth or reproductive performance of parental animals and offspring over three generations. Non-GLP study
Multigeneration reproductive toxicity (dietary) Rat, FDRL PMRA# 2502367	Nicarbazin was added to the diet as a 3:1 mixture of DNC and HDP. Parental and Offspring NOEL= 400 mg/kg bw/d (the highest dose tested) No adverse effects on growth or reproductive performance (fertility, gestation, viability, and lactation and litter size) over three generations. Non-GLP study
Genotoxicity	
Reverse mutation assay in bacteria *Salmonella typhimurium* strains TA1537, TA1535, TA98, and TA100, with and without metabolic activation	Test substances: Nicarbazin (purity not stated) in DMSO at 2000, 1000, 500, 300, and 100 µg/plate HDP (purity not stated) in DMSO at 2000, 1000, 600, and 200 µg/plate DNC (purity not stated) in DMSO at 2000, 1000, 500, 300, and 100 µg/plate.

Study Type/Animal/PMRA #	Study Results
PMRA#2502675	Solubility problems with nicarbazin (2000 µg) and DNC (1000 µg, 2000 µg); both precipitated at >300 µg. Nicarbazin, DNC and HDP were non-mutagenic. Non-GLP study
In vitro gene mutation Rec-assay with *Bacillus subtilis* H-17 (rec+) and M-45 (rec-). Reverse mutation assay in *Escherichia coli* strains WP2hcr+ and WP2 hcr-, and in *Salmonella typhimurium* strains TA1535, TA100, TA1537, TA1538, and TA98 PMRA# 2502368	Nicarbazin was non-mutagenic in the rec-assay with *Bacillus subtilis* H-17 (rec^+) and M-45 (rec^-). Nicarbazin was weakly mutagenic in TA1538 and TA98 without metabolic activation in the bacterial reverse mutation assay. Non-GLP study
Reverse mutation assay in *Escherichia coli* strains WP2hcr+ and WP2 hcr-, and in *Salmonella typhimurium* strains TA1535, TA100, TA1537, TA1538, and TA98 PMRA# 2648955	Precipitation was observed at 1000µg/plate. Nicarbazin was weakly mutagenic in TA98 without metabolic activation.
Mouse lymphoma assay L5178Y cell line, clone 3.7.2.C PMRA# 2648956	No evidence of mutagenicity or clastogenicity.
Micronucleus assay (*in vivo*) Mouse (CRJ:CD-1) PMRA# 2502369	Not genotoxic.
Ex vivo unscheduled DNA (USD) synthesis Hepatocytes of male Fischer rats treated (oral) PMRA# 2648957	Not genotoxic.

[1] [^{14}C]-BNPU-nicarbazin is labelled in the N, N'-bis-(4-nitrophenyl)urea (BNPU) moiety. The BNPU moiety is also referred to as 4,4'-dinitrocarbanilide (in other words, DNC)

[2] [^{14}C]-HDP-nicarbazin is labelled in the hydroxydimethyl pyrimidine moiety (in other words, HDP). [also referred to as the 4,6-dimethyl 2-pyrimidiniol moiety]

Table 2 Toxicity Profile of 30% Granulated Nicarbazin Pre-Mix[1]

Study Type/Animal/PMRA #	Study Results
Acute toxicity	
Acute Inhalation Rat, Sprague Dawley PMRA# 2502360	An LC_{50} cannot be calculated.
Eye Irritation Rabbit, New Zealand White PMRA# 2502361	MAS [a] = 2.22/110 MIS [b] = 4.67/110 (24 hours) Mildly irritating (based on irritation at 72-hours)
Dermal Irritation Rabbit, New Zealand White PMRA# 2502362	MAS [a] = 0/8 MIS [b] = 0/8 (1 hour) Non-irritating
Dermal Sensitization (Bheuler Method) Guinea pig/Dunkin-Hartley PMRA# 2502363	Negative Not a dermal sensitizer

[a] MAS = Maximum Average Score for 24, 48, and 72 hours
[b] MIS = Maximum Irritation Score
[1] The test substance was Koffogran, a granular solid containing 4,4'-dinitrocarbanilide (DNC) and 2-hydroxy-4,6-dimethyl pyrimidine dehydrate (HDP) at 24.3–25.5% a.i. absorbed on wheat middlings. This product was considered equal to the manufacturing concentrate

Table 3 Fate and Behaviour in the Terrestrial Environment

Property	Test substance	Value	Transformation products	PMRA document number
Abiotic transformation				
Hydrolysis	DNC HDP	Stable	Not determined	2502373, 2502374
Phototransformation	Nicarbazin, in aqueous solution	Did not breakdown after 24 hours of exposure to light (desert sun)	NA	2502428
Biotransformation				
Biotransformation in aerobic soil	Nicarbazin	DT_{50} 28-119 days; SFO/2 84.5 days; DT_{90} > 364 days	Not determined	2502375, 2502376, 2502400

Mobility				
Adsorption / desorption in soil	DNC	Non-mobile (Binds to soils)	Not determined	2502377
	HDP	Less than moderately mobile		
Volatilization	Nicarbazin	Negligible; Vapour pressure expected to be zero at ambient temperature	Negligible	2502378 2502379
Field studies				
Field dissipation	Nicarbazin	DT_{50} 301 days; Nicarbazin did not leach beyond the top soil layer (15 cm depth)	Not determined	2502378, 2502379

NA = not applicable

Table 4 Toxicity to Non-Target Terrestrial Species

Organism	Exposure	Test substance	Endpoint value	Toxicity Classification[1]	PMRA document number
Invertebrates					
Earthworm *Eisenia foetida*	14d-Acute LC_{50}	Nicarbazin HDP DNC	>1000 mg/kg soil >1000 mg/kg soil >1000 mg/kg soil	NA	2502381
Birds					
Bobwhite quail *Colinus virginianus*	Acute oral LD_{50}/NOEC	Nicarbazin	2250 mg/kg bw	Practically nontoxic	2502391
	5d-Dietary LD_{50} NOEC	Nicarbazin	5625 mg/kg diet 320 mg/kg diet	Practically non toxic	2502392
Mallard duck *Anas platyrhynchos*	5d-Dietary LD_{50} NOEC	Nicarbazin	3738 mg/kg diet 320 mg/kg diet	Slightly toxic	2502393
Mammals					
Rat	Acute oral LD_{50}	Nicarbazin	> 5000 mg/kg bw	Practically nontoxic	2502340
Rabbit- New Zealand White rabbits	28d-Reproduction NOAEL	Nicarbazin	Maternal 60 mg/kg/bw/d Offspring 120 mg/kg/bw/d	NA	2648954
Vascular plants					
Vascular plant	14d-Vegetative vigour	Nicarbazin	Non linear response in oats	NA	2502397

[1] Applicable USEPA toxicity classification scheme; NA = not applicable

Table 5 Toxicity of the Nicarbazin Components HDP and DNC to Non-Target Aquatic Organisms.

Organism	Exposure	Test Substance and Endpoint Value		Toxicity Classification[a]	PMRA document number
		HDP mg/L	DNC mg/L		
Freshwater species					
Daphnia magna	48h-Acute EC_{50} NOEC	>107	>0.093[b] 0.027 (lethargy)	Practically nontoxic	2502383 2502384
Rainbow trout *Oncorhynchus mykiss*	96h-Acute LC_{50} NOEC	>110	>0.069[b] 0.069	Practically nontoxic	2502386 2502387
Bluegill sunfish *Lepomis macrochirus*	96h-Acute LC_{50} NOEC	>122	>0.072[b] 0.072	Practically nontoxic	2502388 2502389
Guppy *Poecilia reticulata*	96h-Acute LC_{50}	>10000	>0.02[b]	Practically nontoxic	2502385
Freshwater alga *Chlorella pyrenoidosa*	96h-Acute EC_{50}	>10000	>0.02[b]	Practically nontoxic	2502385

[a] Applicable USEPA toxicity classification
[b] Highest achievable test concentration due to low solubility of DNC in test solution

Table 6 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes, Non-toxic mode of action
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	No: Half-life (28-119 days)
	Water/Sediment system	Half-life ≥ 182 days (water) ≥ 365 days (sediment)	NA
	Air	Half-life ≥ 2 days or evidence of long range transport	NA: Non-volatile.
Bioaccumulation[4]	Log K_{OW} ≥ 5		No Nicarbazin: NA DNC: Log K_{OW} = 3.6 HDP: Log K_{OW} = -0.94
	BCF ≥ 5000		NA
	BAF ≥ 5000		NA
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgment, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3]If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

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2502344	2014, DACO 2.11 Manufacturing Summary, DACO: 2.11, 2.11.1 CBI
2502345	2015, DACO 2.11.2 Description of Starting Materials, DACO: 2.11.2 CBI
2502346	2015, Raw Material Specs and Methods, DACO: 2.11.2 CBI
2502348	2015, DACO 2.11.4 Discussion of Impurities, DACO: 2.11.4 CBI
2502349	2015, DACO 2.12 Specifications, DACO: 2.12 CBI
2502350	2002, Nicarbazin Specifications, DACO: 2.12 CBI
2502351	2015, DACO 2.13 Preliminary Analyses, DACO: 2.13 CBI
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2502354	2002, 6 Lot Analyses, DACO: 2.13.3 CBI
2502355	2015, DACO 2.14 Chemical and Physical Properties, DACO: 2.14
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2546034	2015, Appendices 1 - 5, DACO: 2.13.1 CBI
2546035	2015, DACO 2.13.2 Confirmation of Identity, DACO: 2.13.2 CBI
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2502493	2015, 3.5 Chemical and Physical Properties, DACO: 3.5
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2502422	2015, DACO 3.3.1 Establishing Certified Limits, DACO: 3.3.1 CBI
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2.0 Human and Animal Health

PMRA Document Number	Reference
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2502364	2004, Nicarbazin Chronic Toxicity Rat, DACO: 4.4.1
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2502368	2004, Nicarbazin Genotoxicity, DACO: 4.5.4
2502369	2001, Nicarbazin Micronucleus Test in Bone Marrow of CD-1 Mice 0 h + 24 h Oral Dosing and 48 h Sampling, DACO: 4.5.5
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3.0 Environment

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4.0 Value

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B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

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